



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/215	A1	(11) International Publication Number: WO 00/04899 (43) International Publication Date: 3 February 2000 (03.02.00)
(21) International Application Number: PCT/US99/16374 (22) International Filing Date: 20 July 1999 (20.07.99) (30) Priority Data: 09/119,951 21 July 1998 (21.07.98) US (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): PONTICELLO, Gerald, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SUGRUE, Michael, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: OPTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION (57) Abstract Combinations of a prostaglandin, prostaglandin derivative, hypotensive lipid derived from a prostaglandin or prostaglandin derivative or an ophthalmologically acceptable salt thereof and a topical carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof are particularly useful in the treatment of ocular hypertension and glaucoma. The combinations are characterized by an improved effect and reduced side-effects.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GK	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

TITLE OF THE INVENTIONOPHTHALMIC COMPOSITIONS FOR TREATING OCULAR
HYPERTENSION

5

BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. The early methods of treatment of glaucoma employing pilocarpine produced undesirable local effects that made this drug, though valuable, unsatisfactory as a first line drug. More recently, clinicians have noted that many β -adrenergic antagonists are effective in reducing intraocular pressure. While many of these agents are effective for this purpose, there exist some patients with whom this treatment is not effective or not sufficiently effective. Many of these agents also have other characteristics, e.g., membrane stabilizing activity, that become more apparent with increased doses and render them unacceptable for chronic ocular use.

Although pilocarpine and β -adrenergic antagonists reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase, and thus they do not take advantage of reducing the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

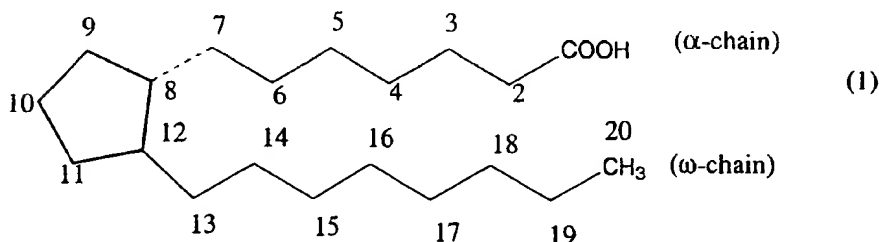
Agents referred to as carbonic anhydrase decrease the formation of aqueous humor by inhibiting the enzyme carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to

- 2 -

treat intraocular pressure by systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such a gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular pressure, or when no other agent is effective.

For several years, the desirability of directing the carbonic anhydrase inhibitor to only the desired ocular target tissue has been recognized. Because carbonic anhydrase inhibitors have a profound effect in altering basic physiological processes, the avoidance of a systemic route of administration serves to diminish, if not entirely eliminate, those side effects caused by inhibition of carbonic anhydrase such as metabolic acidosis, vomiting, numbness, tingling, general malaise and the like. Topically effective carbonic anhydrase inhibitors are disclosed in U.S. Patent Nos. 4,386,098; 4,416,890; 4,426,388; 4,668,697; and 4,863,922 and 4,797,413.

Prostaglandins, or Pgs, are members of a class of organic carboxylic acids that are contained in human and most other mammalian tissues or organs and that exhibit a wide range of physiological activities. Naturally occurring Pgs possess a common structural feature, the prostanoic acid skeleton, depicted in Formula I below:



Some synthetic analogues have somewhat modified skeletons. The primary PG's are classified based on the structural feature of the five-membered cycle moiety into PGA's, PGB's, PGC's, PGD's, PGE's, PGF's, PGG's, PGH's, PGI's and PGJ's and also on the presence or absence of unsaturation and oxidation in the chain moiety as:

Subscript 1 13,14-unsaturated-15-OH,

- 3 -

Subscript 2 5,6- and 13,14-diunsaturated -15-OH,
Subscript 3 5,6-13,14-, and 17,18-triunsaturated-
15-OH

5 Further, PGFs are subclassified as α or β according to the configuration of the hydroxy group at position 9.

Prostaglandins and prostaglandin derivatives are known to lower intraocular pressure. U.S. Patent 4,883,819 to Bito describes the use and synthesis of PGAs, PGBs and PGCs in reducing intraocular
10 pressure. U.S. Patent 4,824,857 to Goh et al. describes the use and synthesis of PGD₂ and derivatives thereof in lowering intraocular pressure including derivatives wherein C-10 is replaced with nitrogen. U.S. Patent 5,001,153 to Ueno et al. describes the use and synthesis of 13,14-dihydro-15-keto prostaglandins and prostaglandin derivatives to
15 lower intraocular pressure. U.S. Patent 4,599,353 describes the use of eicosanoids and eicosanoid derivatives including prostaglandins and prostaglandin inhibitors in lowering intraocular pressure.

Prostaglandin and prostaglandin derivatives lower intraocular pressure by increasing uveoscleral outflow. This is true for
20 both the F type and A type of Pgs and hence presumably also for the B,C,D,E and J types of prostaglandins and derivatives thereof. A problem with using prostaglandin derivatives to lower intraocular pressure is that these compounds often induce an initial increase in intraocular pressure.

25 Since the carbonic anhydrase inhibitor lowers intraocular pressure without accompanying transient ocular hypertension exhibited by the primary PGs, the combination of the carbonic anhydrase inhibitor and the prostaglandin derivative can be used for the treatment of diseases and conditions in which the lowering of intraocular pressure is desired, for example glaucoma, ocular hypertension and other disease
30 accompanied by an increase in intraocular pressure.

Thus, when a carbonic anhydrase inhibitor, which decreases the formation of aqueous humor, is combined with a prostaglandin or prostaglandin derivative, which increases the outflow of aqueous humor,

- 4 -

there is experienced an effect that reduces intraocular pressure below that obtained by either medicament individually.

5 The activity of the carbonic anhydrase inhibitor currently marketed wanes 6 to 8 hours post-dose, meaning that as single agents these carbonic anhydrase inhibitors must be administered at least three times day to maintain the desired lowering of intraocular pressure. The combination of this invention maintains the desired lowering of intraocular pressure for a full twelve hours. Because of this increased duration of action, the combination disclosed herein is effective when administered only twice a day. Patient compliance is anticipated to be greater with twice a day administration than with three times a day administration.

15 The combinations disclosed herein are effective either by co-administration of the medicaments in one solution or as a combined therapy achieved by prior administration of either the carbonic anhydrase inhibitor or the prostaglandin derivative followed by administration of the other solution. The use of a single solution containing both active medicaments is preferred.

20 There exists a patient population who will benefit from a combination where the minimal dosage of one or both of the medicaments is employed, thus minimizing the possibility of the occurrence of undesirable effects of one or both of the medicaments which would be more likely to become apparent with chronic use at the higher dosage.

25

- 5 -

SUMMARY OF THE INVENTION

This invention relates to novel ophthalmic compositions comprising a topical carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof and a prostaglandin or
5 prostaglandin derivative thereof or a hypotensive lipid derived from a prostaglandin or prostaglandin derivative such as a PGF2 α prostaglandin.

In one aspect of the invention a composition comprising 0.025 to 5% (w/w) of a topical carbonic anhydrase inhibitor such as 5,6-
10 dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material and 0.005 to 2% a
15 hypotensive lipid derived from prostaglandins and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material is disclosed. Said composition can optionally contain a gum belonging to the group consisting of gellan gum or xanthan gum.

Another aspect of the invention is concerned with the use of
20 the novel ophthalmic compositions in the treatment of ocular hypertension or glaucoma.

- 6 -

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel ophthalmic combinations comprising a topical carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof and a prostaglandin or prostaglandin derivative thereof, or a topical carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof and a hypotensive lipid derived from a prostaglandin or prostaglandin derivative, which are used in the treatment of ocular hypertension and glaucoma.

- 10 An aspect of this invention is realized when the prostaglandin is
- 11, 15-dipivaloyl PGF_{2α},
 11-pivaloyl prostaglandin F_{2α} hydroxyethyl ester,
 (+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate,
 15 [1α,2β,3α,5α]methyl-5-cis-2-(phenylethylsulfonamidomethyl)-3,5-dihydroxycyclopentyl heptenoate,
 (+)-5-[6-(1-hydroxy)hexyl]-1,3-benzodioxol-5-yl]-pentanol,
 15-pivaloyl PGF_α,
 20 7-[3α,5α dihydroxy-2-(3α-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid,
 isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate,
 (+)-isopropyl fluprostenol;
 25 [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptanoate;
 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF_{2α} esters,
 13,14-dihydro-15-keto-20-ethyl-PGF_{2α} isopropyl ester or
 30 13,14-dihydro-15-keto-20-ethyl-PGF_{2α} isopropyl ester trimethylphenol-1-acetate.

Another aspect of this invention is realized when hypotensive lipids derived from PGF_{2α} prostaglandins, in which the carboxylic acid group on the α-chain link of the basic prostaglandin

- 7 -

structure is replaced with electrochemically neutral substituents, is used. An example of a hypotensive lipid is that in which the carboxylic acid group is replaced with a C₁₋₆ alkoxy group such as OCH₃ (PGF_{2α} 1-OCH₃), or a hydroxy group (PGF_{2α} 1-OH).

5 A further aspect of this invention is realized when the prostaglandin is

[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl)-4-heptanoate;

10 (+)-isopropyl fluprostenol;

or a hypotensive lipid derived from PGF_{2α} prostaglandins and the topical carbonic anhydrase inhibitor is 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-
15 (ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide.

Another embodiment of the invention is concerned with a novel ophthalmic composition comprising an ophthalmologically acceptable carrier, 0.025 to 5% (w/w) of a topical carbonic anhydrase
20 inhibitor, 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride, and its trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material and 0.005 to 2% (w/w) of a prostaglandin and its trans and cis enantiomers, or an ophthalmologically acceptable
25 salt thereof, including racemic material, wherein the prostaglandin is 11, 15-dipivaloyl PGF_{2α}; (+)-isopropyl fluprostenol; or [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl)-4-heptanoate.

30 The term "prostaglandin or prostaglandin derivative", within this invention refers to those naturally occurring prostaglandins that are useful for lowering intraocular pressure, specifically prostaglandins A,B,C,D,E,F and J class as well as synthetically modified prostaglandins including but not limited to 15-keto (oxo group in place

- 8 -

of OH at 15) 13,14-dihydro (single bond in place of double bond between positions 13 and 14), and esters thereof.

Prostaglandins of the F class, particularly $\text{PGF}_{2\alpha}$ derivatives are known to be particularly potent at lowering intraocular pressure. $\text{PGF}_{2\alpha}$ prostaglandin derived hypotensive lipids, in which the carboxylic acid group on the α -chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents, are also known to be particularly potent at lowering intraocular pressure. In particular, the hypotensive lipids intended for the claimed invention are those compounds which increase aqueous humor outflow without any meaningful interaction with the FP prostaglandin receptor and little or no stimulation of the other prostanoid receptors (DP, EP1-4, IP, TP). Examples of such lipids are taught in US Patent Nos. 4,494,274; 5,034,413; 5,656,635; 5,516,791, 5,385,945, 5,688,819, 5,352,708 and 5,607,978 all incorporated herein by reference.

Although Formula I shows a basic skeleton having twenty carbon atoms, the prostaglandin compounds used in the present invention are not limited to those having the same number of carbon atoms. The carbon atoms in Formula (I) are numbered 2 to 7 on the (α -chain starting from the α -carbon atom adjacent to the carboxylic carbon atom which is numbered 1 and towards the five membered ring 8 to 12 on the ring starting from the carbon atom on which the α -chain is attached, and 13 to 20 on the ω -chain starting from the carbon atom adjacent to the ring. When the number of carbon atoms is decreased on the α -chain, the number is deleted in order starting from position 2 and when the number of carbon atoms is increased in the α -chain compounds are named as substituted derivatives having, substituents at position 1 in place of carboxy group at C-1. Similarly, when the number of carbon atoms is decreased in the ω -chain, the number is deleted in order starting from position 20 and when the number of carbon atoms is increased on the ω -chain, compounds are named as substituted derivatives having respective substituent at position 20. Thus, 13,14-dihydro-15-keto-PG compounds having 10 carbon atoms in the ω -chain are 13,14-dihydro-15-keto-20-ethyl PGs. The term

- 9 -

prostaglandin derivative also includes esters of the C-1 carboxyl group, such as the C1-5 alkyl esters.

The hypotensive lipids contemplated by the claimed invention include $\text{PGF}_{2\alpha}$ lipid analogs which, unlike $\text{PGF}_{2\alpha}$, exhibit no meaningful interaction with recombinant or constitutively expressed FP receptors (human, mouse, cat). Further the $\text{PGF}_{2\alpha}$ lipid analogs exhibit only either minimal or absent interaction with other prostanoid receptors (DP, EP_{1-4} , TP). Even with their inability to interact with with prostanoid receptors the subject $\text{PGF}_{2\alpha}$ lipid analogs, having electrochemically neutral substituents, are potent and efficacious at lowering elevated intraocular pressure (IOP). Examples of such lipids are taught in US Patent Nos. 4,494,274; 5,034,413; 5,656,635; 5,385,945, 5,688,819, 5,352,708 and 5,607,978 all incorporated herein by reference. A particular ocular hypotensive agent is referred to as AGN 192024, disclosed in VanDenburgh et al., Investigative Oph. and Vis. Sci. March 15, 1998, Vol. 39, No.4. p. S258 abstract 1177 and at the May 10-15, 1998 Association for Research in Vision and Ophthalmology (ARVO) meeting by Allergan of Irvine, California.

The novel ophthalmic formulations of this invention comprise about 0.025 to 5% (w/w) of the carbonic anhydrase inhibitors discussed herein, preferably 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxides hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxides and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material, usually about 0.5 to 3% (w/w) and more preferably about 0.7 to about 2% (w/w) and about 0.005 to 2.0% (w/w), preferably about 0.1 to 1% (w/w) of the prostaglandin or prostaglandin derivatives discussed herein, preferably 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF_{2a} esters or 13, 14-dihydro-15-keto-20-ethyl-PGF_{2a} isopropyl esters, and more preferably isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate, (+)-isopropyl fluprostenol, [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-

- 10 -

3-furanyl]-4-heptanoate; or 13,14-dihydro-15-keto-20-ethyl-PGF2 α isopropyl ester trimethylphenol-1-acetate, to be administered on a 1 to 2 times a day schedule.

5 A novel method of this invention comprises the topical ocular administration of about 0.025 to about 5 mg per day, preferably about 0.25 to about 3 mg per day of a carbonic anhydrase inhibitor and concomitant, prior, or previous administration of about 0.005 to 2 mg per day, preferably about 0.1 to 1.0 mg per day, of prostaglandin or prostaglandin derivative to each eye.

10 Suitable subjects for the administration of the formulation of the present invention include mammals, primates, man, and other animals, particularly man and domesticated animals such as cats and dogs. For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or
15 solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of each active component or some submultiple thereof.

Typical ophthalmologically acceptable carriers for the novel formulations are, for example, water, mixtures of water and
20 water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary
25 substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and
30 which are non-injurious in use, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzylidodecinium bromide, benzyl alcohol, phenylethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetate, or gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine,

- 11 -

polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetra acetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional
5 phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like.

The formulation may also include a gum such as gellan gum at a concentration of 0.1% to 2% by weight so that the aqueous eyedrops gel on contact with the eye, thus providing the advantages of a solid
10 ophthalmic insert as described in U.S. Patent 4,861,760.

The formulation may also include a gum such as xanthan gum at a concentration of 0.1 to 2%, preferably 0.4 to 0.7%(w/w). Particularly preferred is KELTROL™ xanthan gum from Monsanto Performance Materials. The formulation of the instant invention
15 employing xanthan gum will be a hypotonic solution, with a freezing point depression between about -0.28°C and -0.4°C, and preferably between about -0.31°C and -0.37°C. Alternatively, the hypotonicity of the ophthalmic solutions of the present invention employing xanthan gum will be between about 150 and 215 mOs/kg, and preferably
20 between 170 and 200 mOs/kg. Conventional ophthalmic solutions are usually prepared as isotonic solutions using tonicity adjusting agents as potassium chloride, sodium chloride, mannitol, dextrose and glycerin. An isotonic solution will have a freezing point depression of approximately -0.54 C. Tonicity may also be measured by the
25 osmolality of the solution, an isotonic solution having an osmolality of about 290 milliosmoles per kilogram (mOs/kg).

The pharmaceutical preparation may also be in the form of a solid insert such as one which after dispensing the drug remains essentially intact as described in U.S. Patents 4,256,108; 4,160,452; and
30 4,265,874; or a bio-erodible insert that either is soluble in lacrimal fluids, or otherwise disintegrates as described in U.S. Patent 4,287,175 or EPO publication 0,077,261.

The pharmaceutical preparation may also be in the form of a suspension utilizing carbonic anhydrase inhibitors (CAI's) having

- 12 -

aqueous solubilities greater than 10 µg/mL but less than 1000 µg/mL at pH 7.4, octanol/water distribution coefficients (DC) measured at pH 7.4 of from 1.0 to 150 and dissociation constants (K_i) of 1.0 nM or lower.

The aqueous solubility is measured, for example, by mixing the CAI, in its neutral or salt form in 0.1M phosphate buffer at a pH of 7.4. The mixture is then agitated for approximately 16 to 24 hours, while maintaining a pH of 7.4. If the mixture is a solution, a small amount of a seed crystal of the neutral CAI is added and the mixture is stirred for approximately 16 to 24 hours. The solid/liquid mixture is filtered through a 0.45 µm filter and the filtrate is assayed by HPLC against standards. The solubility as measured includes both the neutral and ionized forms of the CAI. Under these conditions, at pH 7.4, the CAI's employed for the suspension are predominantly unionized, with the possibility of 10 to 20% of the anionic sulfonamide present (depending on the pKa of the primary sulfonamide group). By way of an example, the suspension encompassed within the meaning of this invention is one which comprises 0.1-10.9 wt% of a carbonic anhydrase inhibitor and 0.01-10.0 wt.% of a polyethoxylated derivative of castor oil resulting from the reaction of from 2-200 moles of ethylene oxide per 1 mole of castor oil, wherein the derivatives can be hydrogenated.

The measure of the dissociation constant is determined using the fluorescence competition assay which uses the fluorescent HCAII:dansylamide complex and is well known in the art, Chen et al., J. Biol. Chem., 242, 5813 (1967) and Ponticello et al., J. Med. Chem., 30, 591 (1987). The relative K_i s for the suspension are less than 3.3 nM.

The following examples of ophthalmic formulations are given by way of illustration and are not limitative of the invention.

- 13 -

EXAMPLE 1

SOLUTION COMPOSITION		I	II	III
5	(S,S)-(-)-5,6-dihydro-4-ethyl- amino-6-methyl-4H-thieno- [2,3b]thiopyran-2-sulfonamide- 7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	22.26 g	22.26 g	1.113 g
10	(+)-isopropyl fluprostenol; (prostaglandin derivative)	10.0 g	1.0 g	1.0 g
	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
15	Benzalkonium Chloride	0.075 g	0.075 g	0.075
	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
20	Mannitol	16.00 g	21.00 g	35.90 g
	Water for injection q.s. ad.	1000 g	1000 g	1000 g

25

The active compounds, phosphate buffer salts, benzalkonium chloride, and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted 30 to volume. The composition is rendered sterile by

30 filtration through a sterilizing filter.

- 14 -

EXAMPLES 2-6

Following the procedures of Example 1, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

5	Compound	Example No.
10	(S,S)-(-)-5,6-dihydro-4-ethyl-amino-6-methyl-4H-thieno-[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	2
15	(S,S)-(-)- 3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	3
20	R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	4
25	R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	5
	(S,S)-(-)-5,6-dihydro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	6

- 15 -

<u>EXAMPLE 7(Suspension</u>		<u>CONCENTRATION</u>
		<u>(WT/V%)</u>
5	R-(+)-4-ethylamino-3,4-dihydro-2-(3-methoxy) propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide	2%+2% xs
10	13,14-dihydro-15-keto-20-ethyl- PGF ₂ . isopropyl ester (prostaglandin derivative)	0.5%
	Hydroxypropylmethylcellulose	3%
	Dibasic Sodium Phosphate	0.2%
15	Sodium Chloride	0.7%
	Disodium Edetate	0.01%
20	Polysorbate 80	0.05%
	Benzalkonium Chloride	0.01%
	NaOH/HCl	pH adjust
25	Purified Water	q.s. 100%

30 The suspension may be prepared by heating 400 mL of purified water to boiling. HPMC (30.0g) is added and the mixture stirred vigorously until homogeneous. To this is added a solution consisting of sodium chloride (7.0 g), dibasic sodium phosphate (2.0g), disodium edta (0.1g), polysorbate 80 (0.5g) and benzalkonium chloride (10.5 mL of a 1% solution) and purified water is added to a final volume of 900 mL. The mixture is stirred and cooled in an ice bath to room temperature and the pH is adjusted to 7.2 employing HCl (3.5 mL

- 16 -

of a 1 N solution. The mixture is q.s. to the final weight with purified water (total 1010g) and filtered through a 10 micron filter. The formulation is prepared by the addition of the above HPMC vehicle (15.014 g) to the above TCAI (0.3074 g) and prostaglandin (1.0 g) and
5 the mixture is ball milled with 3 mm glass beads (5 g) for approximately 45 hours.

EXAMPLES 8-15

Following the procedures of Example 1, solutions are
10 prepared substituting the compounds below for the prostaglandin derivative

	<u>Compound</u>	<u>Example No.</u>
15	PGF2 α , -l-isopropyl ester	8
	PGA2	9
20	13,14-dihydro-15-keto-PGE2 methyl ester	10
	15-keto-PGF2 α	11
25	PGF2 α tromethamine salt	12
	PGA1	13
30	(+)-isopropyl fluprostenol	14
	[2R(1E, 3R),3S(4Z),4R]-isopropyl- 7-(tetrahydro-2-[4-(3-chlorophenoxy)- 3-hydroxy-1-butenyl]-4-hydroxy-3- furanyl]-4-heptanoate;	15

- 17 -

EXAMPLE 16

SOLUTION COMPOSITION		I	II
5	5,6-dihydro-4-ethylamino 6-methyl-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	2.0 mg	0.2 mg
10	13,14-dihydro-15-keto-20-ethyl- PGF2 α isopropyl ester trimethylphenol-l-acetate	0.1 mg	1.0 mg
15	Gelrite™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate	Quantity sufficient to give .2H ₂ O	
20	Dibasic sodium phosphate .12H ₂ O	final pH	5.5 - 6.0
	Benzyldodecinium bromide	0.10 mg	0.10 mg
25	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, Gelrite' gellan gum, phosphate
buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to
and suspended or dissolved in water. The pH of the composition is
adjusted to 5.5-6.0 and diluted to volume. The composition is rendered
sterile by ionizing radiation.

- 18 -

EXAMPLES 17-21

Following the procedures of Example 16, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

5	Compound	Example No.
	(S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-4H-thien[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	17
10	3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1 dioxide hydrochloride	18
15	R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	19
20	R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	20
25	(S,S)-trans-5,6-dihydro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7- dioxide	21

- 19 -

EXAMPLES 22-29

Following the procedures of Example 16, solutions are prepared substituting the compounds below for the prostaglandin derivative.

	<u>Compound</u>	<u>Example</u>
	PGF2 α , -l-isopropyl ester	22
10	PGA2	23
	13,14-dihydro-15-keto-PGE2 methyl ester	24
15	15-keto-PGF ₂ α	25
	PGF2 α tromethamine salt	26
	PGA ₁	27
20	(+)-isopropyl fluprostenol;	28
	[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptanoate;	29
25		

- 20 -

EXAMPLE 30

SOLUTION COMPOSITION		I	II
5	5,6-dihydro-4-ethylamino 6-methyl-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	2%	2%
10	13,14-dihydro-15-keto-20-ethyl- PGF2 α isopropyl ester trimethylphenol-I-acetate	0.1 %	1.0 %
15	Xanthan gum	0.5%	0.7%
	Sodium Chloride	0.2%	0.2%
	Benzalkonium Chloride	0.0075%	0.0075%
20	Sodium Hydroxide	qs pH5.6	pH 5.6
	Water	qs 100%	100%

25 The active compounds, sodium chloride and benzalkonium chloride are dissolved in water for injection. The pH of the composition is adjusted to 5.6 by addition of 0.2N sodium hydroxide solution, and water for injection is added until the weight of the composition is equal to 75 parts of the final weight (I) or 65 parts of the final weight (II). The composition is sterilized by filtration, and the solution flushed with
30 sterile nitrogen. Then a clarified, steam sterilized concentrate of 2% xanthan gum is added to the solution of drug and the resulting solution is homogenized by stirring. The solution is aseptically subdivided into sterile vials and sealed.

- 21 -

EXAMPLES 31-35

Following the procedures of Example 30, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

Compound	Example No.
(S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	31
3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1 dioxide hydrochloride	32
R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	33
R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	34
(S,S)-trans-5,6-dihidro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7- dioxide	35

30

- 22 -

EXAMPLES 36-43

Following the procedures of Example 30, solutions are prepared substituting the compounds below for the prostaglandin derivative.

	<u>Compound</u>	<u>Example</u>
	PGF2 α -1-isopropyl ester	36
10	PGA2	37
	13,14-dihydro-15-keto-PGE2 methyl ester	38
15	15-keto-PGF ₂ α	39
	PGF2 α tromethamine salt	40
	PGA ₁	41
20	(+)-isopropyl fluprostenol	42
	[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptanoate;	43
25		

- 23 -

WHAT IS CLAIMED IS:

1. An ophthalmic formulation for the treatment of
5 ocular hypertension and glaucoma in a subject in need thereof,
comprising an ophthalmologically acceptable carrier, 0.025 to 5%
(w/w) of a topical carbonic anhydrase inhibitor or its trans and cis
enantiomers, or an ophthalmologically acceptable salt thereof, including
10 racemic material and 0.005 to 2% (w/w) of a hypotensive lipid derived
from a prostaglandin or prostaglandin derivative and their trans and cis
enantiomers, or an ophthalmologically acceptable salt thereof, including
racemic material.
2. The ophthalmic formulation according to claim 1
15 wherein the topical carbonic anhydrase inhibitor is 5,6-dihydro-4-
ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7
dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-
4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their
trans and cis enantiomers, or an ophthalmologically acceptable salt
20 thereof, including racemic material.
3. The ophthalmic formulation according to claim 1
wherein the hypotensive lipid is derived from $\text{PGF}_{2\alpha}$ prostaglandins.
- 25 4. A formulation according to claim 3 wherein the
hypotensive lipid derived from $\text{PGF}_{2\alpha}$ prostaglandins contains
electrochemically neutral substituents in place of the carboxylic acid
group on the α -chain link of the basic prostaglandin structure.
- 30 5. The formulation of Claim 1 wherein the
concentration of carbonic anhydrase inhibitor is 0.5% to 3% and the
concentration of the hypotensive lipid is 0.1% to 1.0%.

- 24 -

6. The formulation of claim 1 wherein the carbonic anhydrase inhibitor has an aqueous solubility greater than 10 ug/mL but less than 1000 ug/mL at pH 7.4, and a K_i of 1.0 nM or lower.

5 7. The formulation of claim 6 which is a suspension.

8. The formulation of claim 1 which optionally contains from about 0.1% to about 2% of gellan gum.

10 9. The formulation of claim 1 which optionally contains from about 0.1% to about 2% (w/w) of xanthan gum.

15 10. The formulation of claim 9 which contains from about 0.4 to about 0.7% (w/w) of xanthan gum, said xanthan gum being a hypotonic solution, with a freezing point depression between about -0.28°C and -0.4°C.

20 11. The formulation of claim 10 wherein the gum is KELTROLTM xanthan gum in a hypotonic solution with a freezing point from about -0.31°C to about -0.37°C.

25 12. An ophthalmic formulation for the treatment of ocular hypertension and glaucoma in a subject in need thereof, comprising an ophthalmologically acceptable carrier, 0.5 to 3% (w/w) of a topical carbonic anhydrase inhibitor or its trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material and 0.1 to 1.0% (w/w) of a hypotensive lipid derived from a prostaglandin or prostaglandin derivative and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including
30 racemic material and a gum belonging to the group consisting of from about 0.1% to about 2% of gellan gum or from about 0.1% to about 2% (w/w) of xanthan gum..

- 25 -

13. A formulation according to claim 12 wherein the carbonic anhydrase inhibitor is 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxido hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxido and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material, the hypotensive lipid is derived from PGF_{2α} prostaglandins contains electrochemically neutral substituents in place of the carboxylic acid group on the α-chain link of the basic prostaglandin structure and the gum is xanthan gum.

14. A formulation according to claim 13 which contains from about 0.4 to about 0.7%(w/w) of xanthan gum, said xanthan gum being a hypotonic solution, with a freezing point depression between about -0.28°C and -0.4°C.

15. The formulation of claim 14 wherein the gum is KELTROLTM xanthan gum in a hypotonic solution with a freezing point from about -0.31°C to about -0.37°C.

16. An ophthalmic formulation for the treatment of ocular hypertension and glaucoma in a subject in need thereof, comprising an ophthalmologically acceptable carrier, 0.025 to 5% (w/w) of a topical carbonic anhydrase inhibitor, 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxido hydrochloride, and its trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material and 0.005 to 2% (w/w) of a prostaglandin and its trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material, wherein the prostaglandin is 11, 15-dipivaloyl PGF_{2α}; (+)-isopropyl fluprostenol; or [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-

- 26 -

(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptanoate.

5 17. A method of treating ocular hypertension and
glaucoma which comprises the topical ocular administration to a patient
in need of such treatment of a unit dose of the formulation of Claim 1.

10 18. A method of treating ocular hypertension and
glaucoma which comprises the topical ocular administration to a patient
in need of such treatment of a unit dose of the formulation of Claim 7.

15 19. A method of treating ocular hypertension and
glaucoma which comprises the topical ocular administration to a patient
in need of such treatment of a unit dose of the formulation of Claim 12.

20. A method of treating ocular hypertension and
glaucoma which comprises the topical ocular administration to a patient
in need of such treatment of a unit dose of the formulation of Claim 16.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/215

US CL : 514/530, 573

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/530, 573

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,811,443 A (DESANTIS, Jr. et al.) 22 September 1998, see the entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

A	document defining the general state of the art which is not considered to be of particular relevance	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E	earlier document published on or after the international filing date	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O	document referring to an oral disclosure, use, exhibition or other means	*A*	document member of the same patent family
P	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 SEPTEMBER 1999	Date of mailing of the international search report 08 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>[Signature]</i> ZOHREH FAY Telephone No. (703) 308-1235

THIS PAGE BLANK (USPTO)